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*Exhange
Committee*

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Dr. Aaron Shatkin
Roche Institute of Molecular Biology
Nutley, New Jersey 07110

Dear Aaron,

Since I was not present at your meeting, I had to collect my own thoughts first, before I came to any position.... I am enclosing the summary of what I think about the problem in general. As to positions:

- (1) There is a defined risk since we cannot assess contamination rate.
- (2) With respect to my own parochial interests, I have no knowledge as to whether herpesviruses are oncogenic. I must presume for the purposes of discussion that they are.
- (3) Although I am willing to abide by the moratorium, it is in principle undesirable for reasons stated.
- (4) I would recommend assignment of a moderate to high risk classification to these studies. I further would suggest that their performance be licensed based on assessment of available facilities and absolute need, i.e., only when it becomes abundantly clear that no other approach is feasible.
- (5) I have little faith in institutional review committees. They either take themselves too seriously or are a farce. I would prefer to see a panel associated with the National Academy of Sciences or the National Science Foundation but not by a study section or another NIH Committee. A single body should suffice. Proliferation of bodies conferring approval or disapproval, as the case might be, would lead to a terrible mess.

With best regards,

Sincerely yours,

B
Bernard Roizman

BR/nc

In principle, a proposal for a voluntary moratorium on certain kinds of experiments with recombinant molecules for the purpose of ascertaining their safety is reasonable and laudable. Inherent in this proposal however are two propositions. The first proposition is that there is a reasonable probability that such experiments might be dangerous and that the assessment of this probability arises from the cumulative experience of a century of Microbiology as a Science. The second proposition is that safety of experiments of this nature is testable. A closer look at these two propositions does in fact show a hierarchy, for even if the first were to be discredited as unfounded, the moratorium will remain in effect until the safety of these experiments can be tested. It is convenient at this point to discuss the propositions first, and their hierarchical implications second.

The Foundations

In preface, the proposition that meddling with Nature could unleash a monster detrimental to humanity has persisted since biblical times not only among the ignorant but also among the learned. If Lewis Mumford's interpretation of a passage in Leonardo di Vinci's notebooks is correct, even he feared science as an irresistible monster against whom the population defended itself in vain. The notion persists in countless science fiction books. Also in countless books it has been dealt with at a more serious level by numerous scientists of which Bronowski, Dubois and Waddington are just a few. To exercise restraint, we have three questions. The first is whether contamination of the experimenter with the agent being investigated occurs, can it be measured and is it a potential threat to mankind. The answer is a qualified yes. There have been a large number of documented laboratory accidents harmful to the investigator, probably even more undocumented cases, and at least in one instance I know of, the agent has spread from the investigator to another individual. In this instance, a technician working with Small Pox in England became infected and passed the virus to another patient in the same hospital ward. Although precise documentation is lacking, we must assume that this is a possible and very likely a probable occurrence. Suffice it to mention that tuberculosis was an occupational disease among pathologists and although we might make a distinction between that occupational disease and another one, namely venereal herpes among prostitutes, elimination of infection would require working conditions which would render the exercise of these professions difficult. The point to be made is that there are occupational hazards involving microorganisms. Although we can list dangerous viral, rickettsial, bacterial and mycotic agents, the hierarchy would most likely reflect not the probability of infection but rather their virulence. We can say for example that Salmonella is more dangerous than E. coli but only because the former is more virulent. However, the problem we are concerned with is not virulence but laboratory infection even if it does not lead to clinical manifestations. From this point of view just about any organism is potentially dangerous and the potential hazard increases with the capacity of that organism to multiply internally or on any surface of the human body

where it makes contact with human cells.

no — The second question we must ask is whether any organism can be made more virulent than it already exists in Nature. There is not much information on this point but in principle there exists evidence that the virulence of microorganisms in nature cycles, or at least becomes attenuated. Fenner's experience with myxomatosis is a case in point. Syphilis was once far more virulent than it is today. If we assume that virulence of certain organisms is not at a maximal point, it is conceivable that experimentation could in fact increase the level of virulence. Except for situations in which increased virulence was specifically selected for, I do not know of a specific instance in which a manipulation involving mutagenization yielded such mutants. If we agree that the trend in nature is toward attenuation of microorganisms including viruses and that laboratory contamination is a common event, the specter of the Munfordian monster hangs heavy on anyone working on modification of genetic content of any organism since it is likely that the information for virulence is at least in part preserved. The fact that such monsters have not arisen, or we have not heard of them, does not exclude the possibility that they might arise.

Finally the question arises whether genetic information could become transferred from a bacterium to a cell. Irrespective of whether the virulence of a bacterium is diminished or accentuated by the introduction of a foreign piece of genetic material there is no way to exclude even the most bizarre ad hoc models of such an occurrence.

To summarize a lengthy recital, laboratory contamination probably occurs more often than has been documented and infection may well spread. Although we have not seen increased virulence as a consequence of non-selective genetic manipulation, it cannot be excluded. In this instance, virulence should be considered as synonymous with increased ability to multiply in or on humans as well. Nothing in the repertoire of Microbiology as a Science excludes the Munfordian monster even though to date we have scant evidence of it.

The Tests

The idea of testing of recombinant molecules from the point of view of safety is superficially attractive, but in practical terms it succumbs rapidly of its own weight. The problem is not that a given recombinant molecule could not be tested rapidly, but rather, that not all combinations and permutations of molecules could be tested. Moreover, the test in an experimental animal is not per se sufficient evidence that a given molecule is harmless to humans. The point in issue is that a satisfactory test involves the preparation of a myriad of recombinant molecules in rather large amounts. In point of fact, this is precisely the objective of many experiments involving recombinant molecules.

The Dilemma

If we accept the proposition that Science cannot exclude the monster and that a test of its existence is tantamount to actually doing the experiments, with all attendant risks, we have almost no choice but to extend the

moratorium indefinitely. On philosophical grounds this is not a practical solution.

The concept of an indefinite moratorium implies not self-restraint but active censorship. The argument that the risk attendant these experiments are sufficient to deter any rational experimenter presumes too much. Poison gases and bacteriological warfare agents were developed by perfectly rational experimentalists. Since a project must be funded in order to be carried out, and the results made public to receive the recognition and approbium of the scientific community, it is clear that the moratorium is enforced by an appeal to reason and the threat of a heavy stick. Although the penalty will not be as severe as that faced by Galileo, it may also be that a modern Galileo by virtue of his stature may not suffer at all. Censorship has never been effective in Science as either the Grand Inquisitors or Lysenko could testify, were they alive today. My personal fear of another Copernicus publishing his results post mortem is not that he will show that our fears are groundless but rather that he will unleash the very monster we fear because the scientific community, in denying him the right to do the experiments, will also refrain from providing him with the facilities necessary to do them properly. That a Copernicus will arise is a prediction based on historical principals; we cannot doubt either that he was or will be born.

If we accept the principle that censorship in Science does not work and that most laboratories dealing with nucleic acids do or will have the competence to do such experiments, the solution might be to license them under tightly regulated condition. Regulation is not equivalent to censorship. There is a distinction between an aspiration to meet a set of stringent requirements in order for such experiments to be done, and a total prohibition. This could be done in the following steps.

(i) Set up rigid minimal criteria of safety for the conduct of such experiments.

(ii) Applicants applying for license to perform such experiments should provide certification that appropriate facilities exist, and detail protocols of the purpose and design of these experiments.

(iii) The authority for licensing should not rest upon the institution in which the work is being done since the standards will vary greatly.